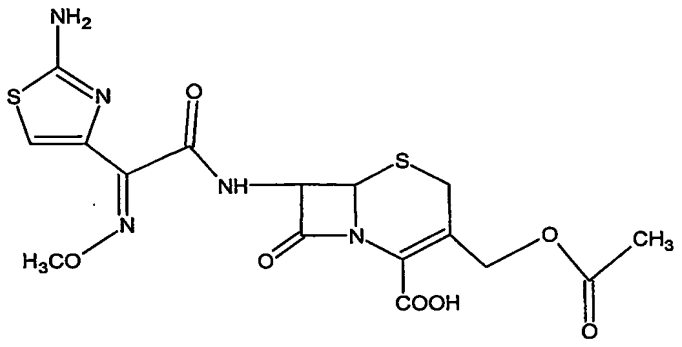
PROCESS FOR THE PREPARATION OF CEPHEM CARBOXYLIC ACIDS

Field of the Invention

The field of the invention relates to processes for the preparation of cephem carboxylic acids. More particularly, it relates to the preparation of ceftriaxone and cefotaxime and pharmaceutical compositions that include the ceftriaxone and cefotaxime.

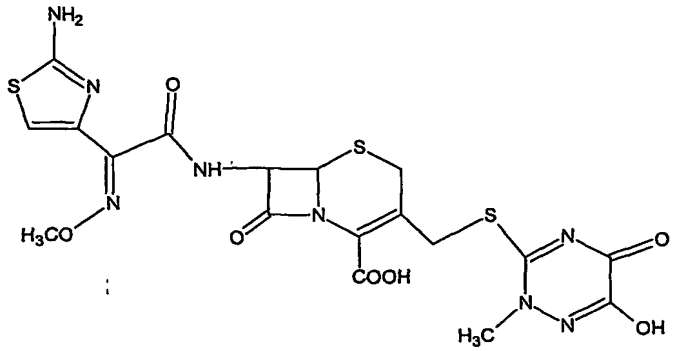
Background of the Invention

Chemically, cefotaxime is [(6R-[6α,7β(Z)]]-3-acetoxymethyl-7-[2-(2-aminothiazol-4-yl)-2-methoxyimino) acetamido]-3-cephem-4-carboxylic acid having Formula I, and is known from U.S.Patent No. 4,152,432.



Formula I

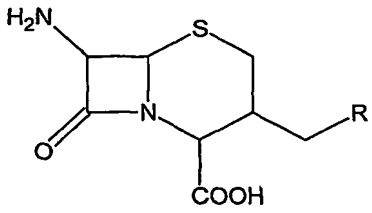
Chemically, ceftriaxone is [(6R-[6α,7β(Z)]]-7-[2-(2-aminothiazol-4-yl)-2-methoxyimino)acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)-thio]methyl]-3-cephem-4-carboxylic acid having Formula II, and is known from U.S.Patent No. 4,327,210.



Formula II

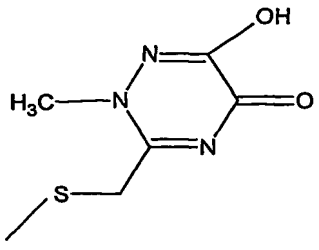
Cefotaxime sodium and Ceftriaxone sodium are semi-synthetic, broad-spectrum cephalosporin antibiotics for parenteral administration characterized by activity against gram-positive and gram-negative microorganisms.

Several processes have been reported for the preparation of cephalosporin antibiotics for example, in U.S. Patent Nos. 4,409,215; 5,109,131; GB 2012276 and WO 00/63214. However, attempts for extending these processes for preparing cefotaxime sodium or ceftriaxone sodium at an industrial scale did not give desired results with respect to yield and quality. More particularly, the synthetic process involving coupling of reactive acid derivative of compound of Formula III,



Formula III

wherein R is



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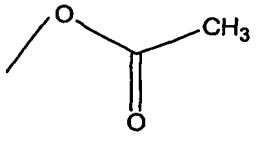
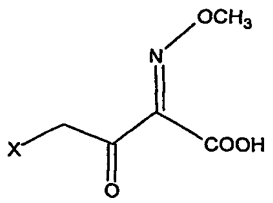
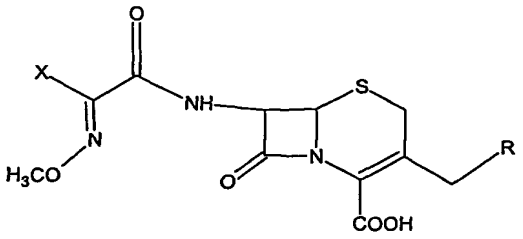


with a reactive derivative of an open chain compound of Formula IV,



Formula IV

wherein X is a halogen, and represents chloro, bromo, or iodo group, to get a compound of Formula V,



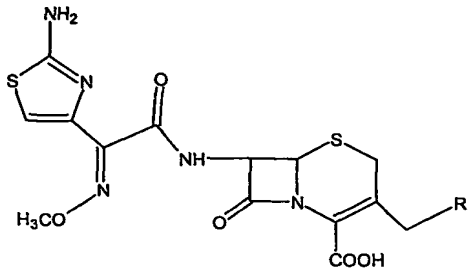
Formula V

wherein R is as defined above, and its subsequent cyclization with thiourea to obtain cefotaxime or ceftriaxone, was found to be unsatisfactory at a commercial scale. Processes described in U.S. Patent No. 4,409,215 and GB 2012276 require protection at the carboxylic position of the compound of Formula III followed by the steps of coupling, cyclization and hydrolysis to get the cefotaxime or ceftriaxone. The additional steps of protection and deprotection result in low yields and high costs. The processes described in WO 00/63214 and U.S. Patent No. 5,109,131 require formation of compound of Formula V as above and its subsequent cyclization with thiourea in a mixture of organic solvent and water to afford cefotaxime or ceftriaxone. Cefotaxime or ceftriaxone thus obtained is of poor quality and contains anti-isomer as a major impurity.

Hence, none of the processes heretofore described are completely satisfactory for various reasons.

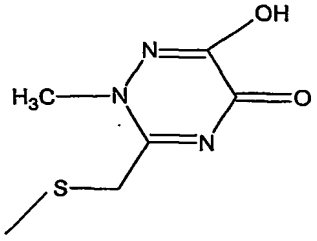
Summary of the Invention

In one general aspect there is provided a process for the preparation of compound of Formula VI, or a salt thereof,



Formula VI

wherein R represents



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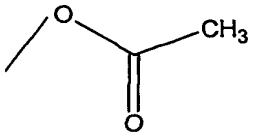
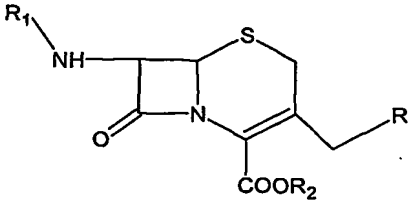
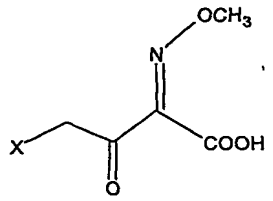


The process includes reacting a compound of Formula VII,



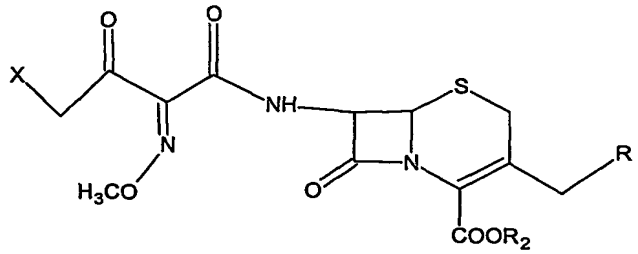
Formula VII

wherein R_1 represents hydrogen or a silyl group, R_2 represents a silyl group or $COOR_2$ represents a carboxylic acid salt, and R is as defined above, with a compound of Formula IV or its reactive acid derivative,



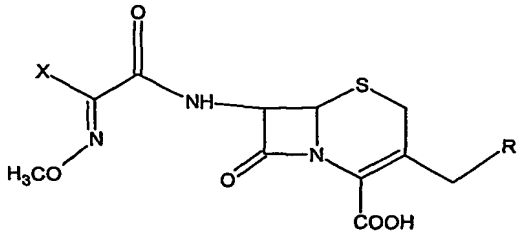
Formula IV

wherein X represents halogen, to obtain a compound of Formula VIII,



Formula VIII

wherein X, R and R_2 are as defined above, desilylating or acidifying the compound of Formula VIII to get a compound of Formula V,



Formula V

wherein X and R are as defined above, and reacting the compound of Formula V with thiourea in aqueous medium in the presence of a weak base, and isolating the compound of Formula VI, or its salts.

The process may include further drying of the product obtained.

In another general aspect there is provided a process for the preparation of compound of Formula V, wherein X and R are as defined above. The process includes reacting a compound of Formula VII, wherein R_1 represents hydrogen or a silyl group, R_2 represents a silyl group or $COOR_2$ represents a carboxylic acid salt, and R is as defined above, with a compound of Formula IV or its reactive acid derivatives, wherein X represents halogen, to obtain a compound of Formula VIII, wherein X, R and R_2 are as defined above; desilylating or acidifying the compound of Formula VIII to get the compound of Formula V.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of compound of Formula VI or a salt thereof; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of Invention

The inventors have developed an efficient process for the preparation of compounds of Formula VI, or a salt thereof, wherein R is as defined above. The process includes reacting a compound of Formula VII, wherein R_1 represents hydrogen or a silyl group, R_2 represents a silyl group or $COOR_2$ represents a carboxylic acid salt, and R is as defined above, with a compound of Formula IV or its reactive acid derivative, wherein X represents halogen, to obtain a compound of Formula VIII, wherein X, R and R_2 are as defined above; desilylating or acidifying the compound of Formula VIII to get a compound of formula V, and reacting the compound of Formula V with thiourea in aqueous medium in the presence of a weak base, and isolating the compound of Formula VI, or its salts.

The carboxylic acid salts of the compound of Formula VII include salts with metals such as sodium and potassium, or salts with organic amines such as triethylamine, pyridine, diclyclohexylamine, and N, N-dimethylaniline.

R_1 and R_2 in the compound of Formula VII may be silyl groups which may be same or different. Suitable silyl groups include trialkyl silyl groups wherein the alkyl substitutents may be same or different. Examples of alkyl substituents include methyl, ethyl, isopropyl, and tert-butyl. Examples of silyl groups include trimethylsilyl and tert-butyldimethylsilyl.

X in the compounds of Formula IV, V and VII is halogen. The term "halogen" includes chloro, bromo, and iodo groups.

The reactive acid derivatives of the compound of Formula IV include acid halides, acid anhydrides, mixed acid anhydrides, reactive esters, reactive amides and the acid azides. Examples of mixed acid anhydrides include anhydrides with lower alkanoic acids such as pivalic acid, trichloroacetic acid or anhydride with a carbonic acid such as monomethylcarbonate. Examples of reactive esters include p-nitrophenylester, N-hydroxysuccinimido ester, N-hydroxyphthalimido ester, 2-mercaptobenzothioazolyl ester and 2-mercapto-5-methyl-1,3,4-thiadiazolyl ester. In particular, the reactive acid derivatives of Formula IV are acid halides.

When the compound of Formula IV is employed in the form of a free acid, the reaction may be carried out in the presence of a condensing agent such as dicylohexylcarbodiimide or a Vilsmeier reagent which may be prepared, for example from dimethylformamide and phosphorous oxychloride.

When the reactive derivative of the acid of Formula IV is employed, the use of such a condensing agent is not required, however, the reaction may be carried out in the presence of a base which may be an alkali metal compound such as sodium bicarbonate, sodium carbonate and potassium carbonate or an organic amine such as triethylamine, lutidine, and pyridine.

In general, the reaction of compound of Formula VII with a compound of Formula IV may be carried out in the presence of a suitable solvent. When R_1, R_2, or both are silyl groups in the compound of Formula VII, suitable solvents for the reaction include

halogenated hydrocarbons such as methylene chloride, hydrocarbons such as toluene, ethers such as tetrahydrofuran, or polar solvents such as dimethylformamide, or a mixture thereof. When R_1 is hydrogen and $COOR_2$ is a carboxylic acid salt in the compound of Formula VII, suitable solvents for the reaction includes methanol, ethanol, acetonitrile, dimethylformamide, water, or a mixture thereof.

The starting compounds of Formula VII, wherein R_1, R_2 or both are silyl may be obtained by silylating the corresponding 3- acetoxymethyl-7-amino-3-cephem-4-carboxylic acid of Formula III with a suitable silylating agent. Examples of silylating agents include halosilanes such as trimethylsilylchloride (TMCS), dimethyldichlorosilane (DMDCS), silylated amides such as N, 0-bistrimethylsilyl acetamide (BSA), silazanes such as 1,1,1,3,3,3-hexamethyldisilazane (HMDS), silylated ureas such as N, N'-bis-(trimethylsilyl) urea (BSU), or a mixture thereof.

When $COOR_2$ is a carboxylic acid salt in the compound of Formula VII, it may be obtained in a conventional manner, for example by treatment of compound of Formula III with a base such as sodium bicarbonate, triethylamine, etc.

The compounds of Formula III and IV may be obtained by methods known in the art, for example methods described in U.S. Patent Nos. 5,109,131; 5,095,149; 4,327,210; 6,448,393; and GB 2,012,276.

The desilylation step of a compound of Formula VIII (wherein R_2 is a silyl group) may be carried out according to conventional methods such as treatment with methanol / water.

The compound of Formula V may be isolated. It may be important to isolate the compound of Formula V to remove the impurities and to obtain the desired compound of Formula VI in high yields and good quality.

The reaction of a compound of Formula V with thiourea may be carried out in the presence of a weak base such as sodium acetate and sodium bicarbonate in aqueous medium. The aqueous medium includes one or more of solvents. Examples of solvents include water, solvents such as ethanol, methanol, isopropanol, acetone, tetrahydrofuran, acetonitrile, N, N-dimethylformamide, or a mixture thereof. The compound of Formula V may be added to aqueous solution of the weak base at a temperature of from about 0°C to

about 15°C. Thereafter, an aqueous solution of thiourea may be added to the above mixture at a temperature of from about 0°C to 15°C. The reaction may then be carried out at a temperature of from about 0°C to 60°C, for example at 0°C to about 25°C, or at 10°C to about 25°C. The compound of Formula VI may be obtained after acidifying the aqueous layer to a pH of about 2.5 to 3.

The compounds of Formula VI may thus be obtained in good yield and purity.

The reaction of compound of Formula V with thiourea may be carried out in water and isolated as IPA or THF solvates in good yields.

The compound of Formula VI so obtained may be converted to its salts by methods known in the art such as by reaction with sodium acetate in ethanol to get its sodium salt.

The inventors also have developed pharmaceutical composition that includes a therapeutically effective amount of compound of Formula VI or a salt thereof; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of cefotaxime Sodium

(i) 3-acetoxymethyl-7-[4-bromo-3-oxo-(Z)-2-methoxyiminobutyrylamino]- 3-cephem-4-carboxylic acid

Solution A

Hexamethyldisilazane (82.8g) and acetamide (60.7g) were refluxed in dichloromethane (800ml) in the presence of a catalytic amount of imidazole (1.0g). The mixture was cooled to 20 to 25°C and 3-acetoxymethyl-7-amino-3-cephem-4-carboxylic acid (100.0g) was added to the resulting solution and refluxed for 1 hour to obtain almost a clear solution. The solution was cooled to 5 to 10°C.

Solution B

Phosphorous pentachloride (74.3g) was added to a solution of 4-bromo-2-methoxyimino-3-oxobutyric acid (78.2g) in dichloromethane (100 ml) at about -20 to -10°C and stirred

for about one hour at the same temperature. The mixture was cooled to -65 to -70°C and acetamide (65g) was added.

Preparation of 3-acetoxymethyl-7-[4-bromo-3-oxo-(Z)-2-methoxyiminobutyrylamino]- 3-cephem-4-carboxylic acid

Solution A was added to solution B at about -70 °C and the temperature was slowly raised to -15 to -20°C in 40 minutes. The mixture was further stirred at about -15 to -10°C for 30 minutes. The reaction mixture was then poured into a mixture of water (1000 ml) and methanol (1000 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (200ml). The combined organic layer was washed with water (250ml) and concentrated under reduced pressure. Cold toluene (1000 ml) was added to the residue and the slurry stirred for 30 min. The product was filtered and washed with toluene (500ml). The solid obtained was then suspended in dichloromethane (500ml) and stirred for 90 minutes. The product was filtered washed with dichloromethane and dried to yield 140 g of the title compound.

(ii) 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid, isopropyl alcohol solvate (1:1)

3-acetoxymethyl-7-[4-bromo-3-oxo-(Z)-2-methoxyiminobutyrylamino]-3-cephem-4-carboxylic acid (50g) obtained from step (i) was added to a solution of sodium acetate (85.3g) in water (500ml) at 10 to 15°C. Thereafter, a solution of thiourea (9.5g) in water (130 ml) was added to it. The mixture was stirred at 20 to 25°C for about one hour. The reaction mixture was then treated with activated carbon (5g) for 15 minutes, filtered, washed with water and diluted with isopropyl alcohol (200 ml) and pH of the aqueous layer was adjusted to about 2.8 to 3.0 with 6N hydrochloric acid. The mixture was cooled to 0 to 5°C and stirred for one hour to obtain cefotaxime as the isopropyl alcohol solvate (35g; purity by HPLC = 99%) after filtration and drying at 45-50°C.

(iii) 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4- carboxylic acid, sodium salt (Cefotaxime sodium)

Preparation of sodium 2-ethylhexanoate solution

Sodium hydroxide (4g) was dissolved in methanol (30ml), cooled to 25°C and ethyl 2-hexanoic acid (12.2g) was added to it in 5 to 10 minutes at 25 to 30°C. The solution was diluted with ethyl acetate (25ml).

Preparation of cefotaxime sodium

Cefotaxime: isopropyl alcohol solvate (1:1, 25g) was suspended in methanol (75ml) at 0 to 5°C, and triethylamine (5g) solution in methanol (20ml) was added to it at the same temperature in 10 minutes. The solution was treated with activated carbon (5g) for 30 minutes, filtered and washed with methanol (35ml). The above solution of sodium 2-ethylhexanoate was added to the combined filtrate at 4 to 7°C. The mixture was stirred for 20 minutes at 4 to 5°C, ethyl acetate (100ml) was added to get turbidity in the solution and the stirring continued at the same temperature for 25 minutes. Ethyl acetate (475ml) was added in 35 to 40 minutes at 4 to 5°C and the stirring further continued at the same temperature for 60 minutes to obtain cefotaxime sodium (21.5g; purity by HPLC = 98.6%) after filtration and drying at 45-50°C.

Example 2: Preparation of ceftriaxone disodium

(i) 7-[4-bromo-3-oxo-(Z)-2-methoxyiminobutyrylamino]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid

Solution A

Hexamethyldisilazane (12.7g) and acetamide (21.6g) were refluxed in dichloromethane (160ml) in the presence of a catalytic amount of imidazole (0.2g) for two hours. The mixture was cooled to 20 to 25°C and 7-amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid (20.0g) was added to the resulting solution and refluxed for 1 hour to obtain almost a clear solution. The solution was cooled to 0 to -5°C.

Solution B

Phosphorous pentachloride (12g) was added to a solution of 4-bromo-2-methoxyimino-3-oxobutyric acid (12.6g) in dichloromethane (160 ml) at about -20 to -10°C and stirred for

about one hour at the same temperature. The mixture was cooled to -60 to -65°C and acetamide (9.7g) was added.

Preparation of 7-[4-bromo-3-oxo-(Z)-2-methoxyiminobutyrylamino]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid.

Solution A was added to solution B at about -65 °C and the temperature was slowly raised to -15 to -10°C in 40 minutes. The mixture was further stirred at about -15 to -10°C for 30 minutes. The reaction mixture was then poured into a mixture of water (200 ml) and methanol (50 ml). The organic layer was separated and stirred with a solution of sodium bicarbonate (20g) in water (300ml). The aqueous layer was separated.

(ii) 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid (ceftriaxone)

A solution of thiourea (5.0g) in water (50 ml) was added to the aqueous layer from step (i) above. The mixture was stirred at 20 to 25°C for about one hour. The reaction mixture was then treated with activated carbon (2.0g) for 15 minutes, filtered, washed with water and pH of the aqueous layer was adjusted to about 2.5 to 2.8 with 6N hydrochloric acid. The mixture was cooled to 0 to 5°C and stirred for one hour to obtain ceftriaxone (18 g; purity by HPLC = 99%) after filtration and drying at 45-50°C.

(iii) 7-[2-(aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl-3-cephem-4-carboxylic acid, disodium salt (ceftriaxone disodium)

Ceftriaxone (30g) was suspended in water (150ml) at 0 to 5°C, and triethylamine (10g) was added to it at the same temperature in 15 to 20 minutes. The solution was treated with activated carbon (6g) for 30 minutes, filtered and washed twice with water (30ml each). Solution of sodium 2-ethylhexanoate (21g) in acetone (60ml) was added to the combined filtrate at 15 to 20°C. The mixture was stirred for 20 minutes at 4 to 5°C, acetone (360ml) was added slowly, followed by seeds of ceftriaxone disodium and the stirring continued at the same temperature for 15 minutes. Acetone (540ml) was added in 60 to 80 minutes at 15 to 20°C and the stirring further continued at the same temperature for 15 minutes to

obtain ceftriaxone disodium (25.8g; purity by HPLC = 99%) after filtration and drying at 40-45°C.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.